Design, Synthesis and Properties of New Cyclophanes and Cryptands with Thiophene and Triazine Units

JURY

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PART I: *THIENO[3,2-b]THIOPHENE BASED CYCLOPHANES*

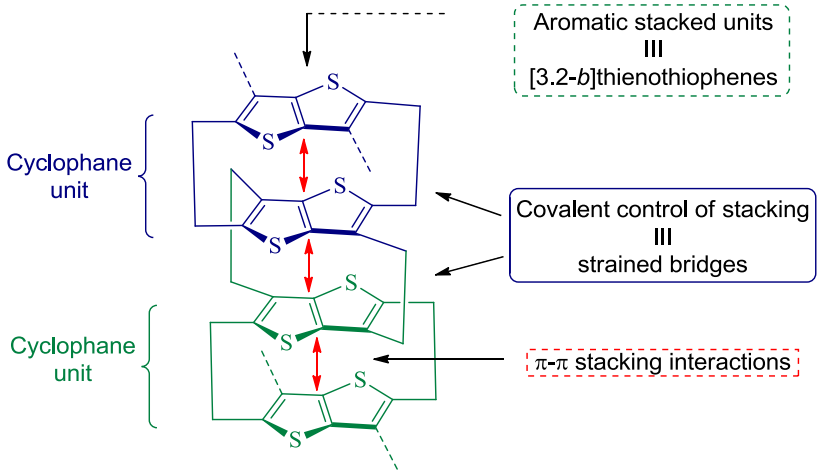
Key Words: thieno[3,2-*b*]thiophene, cyclophanes, π-π stacking

2. ORIGINAL CONTRIBUTIONS

A classical *cyclophane* is a hydrocarbon consisting of an aromatic unit (typically a benzene ring) and an aliphatic chain that forms a bridge between two non-adjacent positions of the aromatic ring. More complex derivatives with multiple aromatic units and bridges forming cage-like structures were developed a long time.

Paracyclophanes were brought to light by Cram and Steinberg[1]in 1951 when [2.2]paracyclophane, the simplest structure of its class, was synthesized.

The goal of this research consists in designing and developing of new cyclophanes based on [3.2-*b*]thienothiophene central units. The purpose is to achieve *stacked thienothiophene-cyclophanes* by ***covalent control*** in order to realize π-π stacking interactions between the aromatic layers. Our objective is to bring in proximity thienothiophene units in a layered manner, held in place by covalent control stacking. The design of these poly-stacked thienothiophene-cyclophanes is inspired from strained structure of [2.2]paracyclophane, and has as purpose to induce inter-cyclic electronic delocalization between different layers (**Scheme 46**).



Scheme 46: Ideal model of poly-stacked cyclophanes with thienothiophene units by covalent control

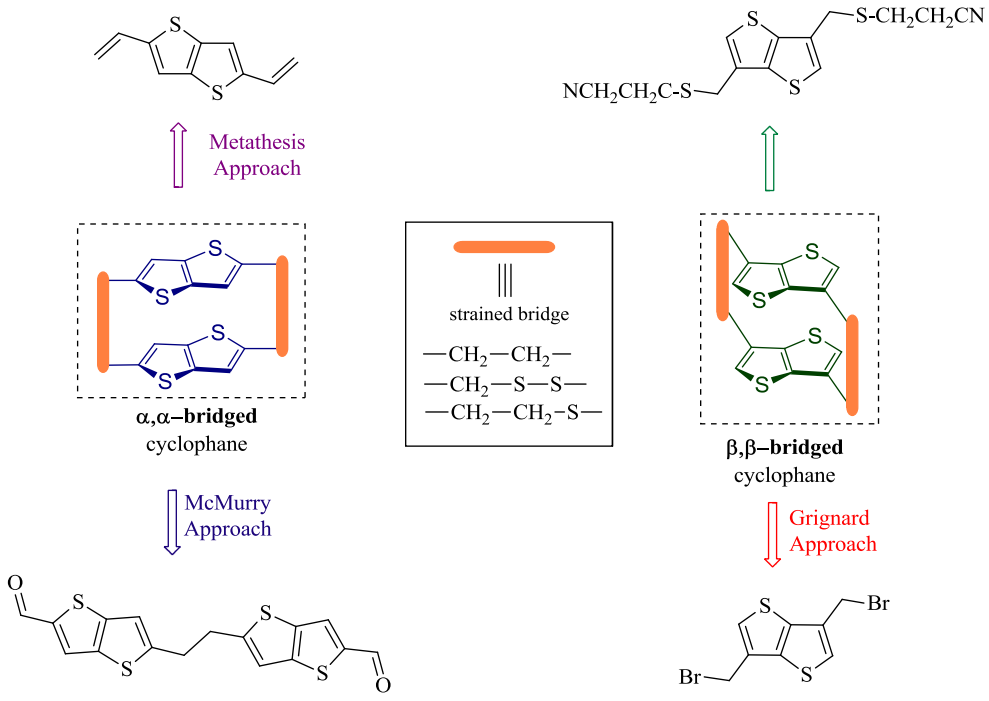
There are some reports, in which metathesis was successfully employed as a key step for the synthesis of cyclophane derivatives.[2] There are also publications in which are methods for the

[1] Cram, D. J., Stenberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691

[2] a) Locke, A. J., Jones, C., Richards, C. J. *J. Organomet. Chem.* **2001**, *637*; b) Smith, A. B., Adams, C. M., Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990; c) Smith, A. B., Kozmin, S. A., Adams, C. M., Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 990; d) Fürstner, A., Stelzer, F., Rumbo, A., Krause, H. *Chem. Eur. J.* **2002**, *8*, 1856; e) Layton, M. E., Morales, C. A.,. Shair, M. D *J. Am. Chem. Soc.* **2002**, *124*, 773; f) Tae, J., Yang, Y. *Org. Lett.* **2003**, *5*, 741; g) Song, D., Blond, G., Fürstner, A. *Tetrahedron* **2003**, *59*, 6899; h) Martinez, V., Blais, J., Astruc, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 4366; i). Martinez, V , Blais, J.-C., Bravic, G., Astruc, D. *Organometallics* **2004**, *23*, 861; j) Watson, M. D., Jäckel, F., Severin, N., Rabe, J. P., Müllen, K. *J. Am. Chem. Soc.* **2004**, *126*, 1402; k) Erker, G., Kehr, G., Fröhlich, R. *J. Organomet. Chem.* **2004**, *689*, 1402; l) Branowska, D., Rykowski, A. *Tetrahedron* **2005**, *61*, 10713; m) Ueda, T., Kanomata, N., Machida, H. *Org. Lett.* **2005**, *7*, 2365; n) Branowska, D., Buczek, I., Kalin'ska, K., Nowaczyk, J., Rykowski, A. *Tetrahedron Lett.* **2005**, *46*, 8539; o) Collins, S. K., Azizi, Y. El *Pure Appl. Chem.* **2006**, *78*, 783; p) Azizi, Y. El, Schmitzer, A., Collins, S. K. *Angew. Chem. Int. Ed.* **2006**, *45*, 968

synthesis of cyclophanes based on the usage of metathesis and Suzuki–Miyaura cross-coupling. Guan and co-workers were the first to use the combination of palladium-catalysed Suzuki–Miyaura cross-coupling and ring-closing metathesis for the efficient synthesis of *m*-terphenyl-based cyclophane, with the aid of Grubbs' 2nd generation catalyst.[3] The synthesis of cyclophane derivatives through a sequence involving Suzuki–Miyaura cross-coupling between α,α-dibromo-*m*-xylene and arylboronic acid derivatives, alkenylation and ring-closing metathesis was reported by Mandal.[4] One of the cyclophanes was obtained by tandem isomerization and metathesis.

Encouraged by literature results concerning approaches leading to cyclophanes McMurry olefination and methathesis are two strategies that we applied in our quest to prepare thienothiophanes along with Grignard approach and a methodologie applied in our laboratory at Angers for the synthesis of crown ethers with bi/ter-thiophene units. As such in **Scheme 47** are presented the strategies that we took in consideration for the synthesis of thienothiophanes bridged in position alpha or beta.



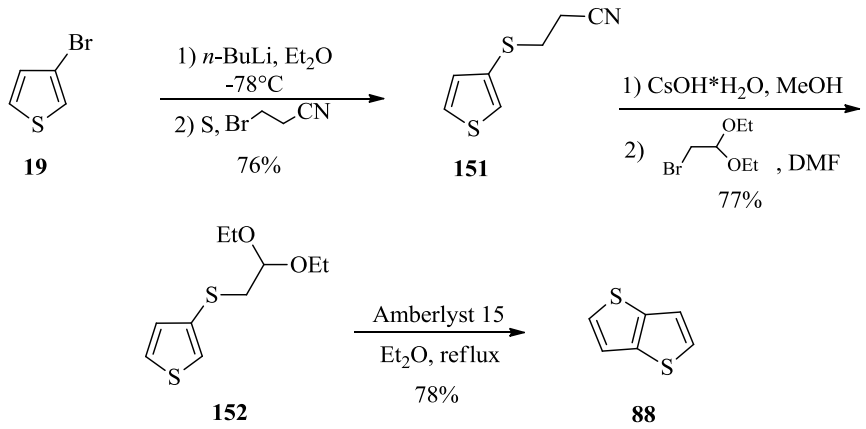
Scheme 47

2.1.1. Synthesis of [3.2-*b*]thienothiophene

In order to synthesized the thieno[3,2-*b*]thiophene we used as starting material 3-bromothiophene which was involved in a lithiation reaction with *n*-BuLi at -78ºC in anhydrous diethyl ether under inert atmosphere. Addition of sulfur and 3-bromoproprionitrile to the lithiated intermediate

[3] Camacho, D. H., Salo, E. V., Guan, Z. *Org. Lett.* **2004**, *6*, 865–868.
[4] Kotha, S., Mandal, K. *Eur. J. Org. Chem.* **2006**, 5387–5393

obtained *in situ* lead to formation of compound **151.** The resulting oil was purified by chromatography on silica gel (eluent: CH_2Cl_2: petroleum ether (1:2)) to give **151** as a yellow oil in 76% yield.



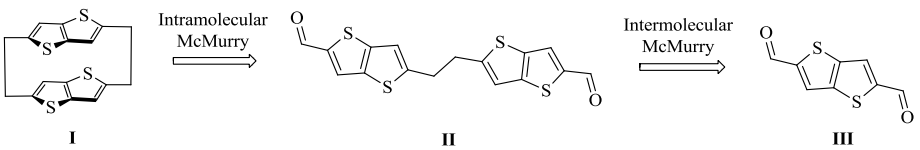
Scheme 48

In the second step compound **151** was involved in a deprotection reaction in presence of cesium hydroxide in anhydrous DMF at room temperature and under inert atmosphere. To the reaction mixture is added bromoacetaldehyde diethyl acetal and stirred overnight.[5] In the third step cyclization reaction is induced in presence of heterogenous acid catalyst. Amberlyst 15 in anhydrous diethyl ether when the central unit thieno[3,2-*b*]thiophene is afforded in good yields.

2.1.2. Synthesis of thienothiophene-cyclophanes

2.1.2.a. McMurry Strategy

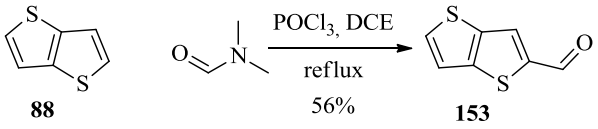
In order to synthesize the cyclophanes with more layers, first we need to obtain the cyclophane with just one layer. At the beginning we had in mind a convergent strategy consisting in two successive McMurry reactions as depicted in **Scheme 49**. This approach involves a first intermolecular McMurry reaction of thienothiophene alpha-alpha di-aldehyde (III), followed by a simple reduction to mono-bridged di-thienothiophene di-aldehyde (II). The later is subjected to a second McMurry reaction but in an intramolecular fashion, and subsequently followed by reduction will possibly lead to the thienothiophene-cyclophane (I).



Scheme 49: McMurry strategy envisioned for thienothiophene-cyclophane

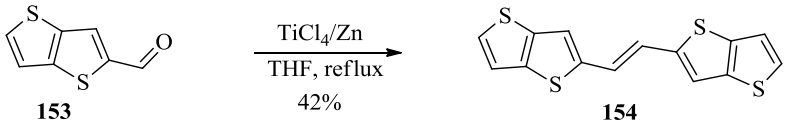
The first step of this strategy consist in a Vilsmeier formylation reaction of the thieno[3,2-*b*]thiophene **88** in the presence of phosphoryl chloride in dry 1,2-dichloroethane and anhydrous DMF at 0ºC under nitrogen atmosphere (**Scheme 51**).[6]

[5] Blanchard, P., Frere, P., Jousselme, B., Roncali J. *J. Org. Chem*. **2002**, *67*, 3961
[6] Blanchard, P., Verlhac, P., Michaux, L., Frere, P., Roncali, J. *Chem. Eur. J.* **2006**, *12*, 1244



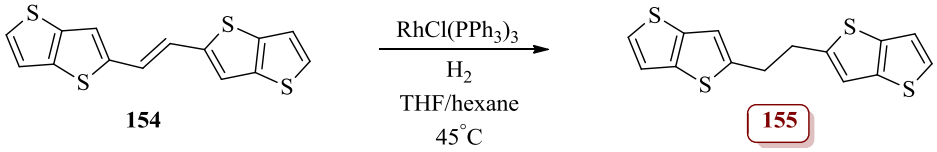
Scheme 51

The McMurry coupling of aldehyde **153** was performed in presence of titanium (IV) tetrachloride in anhydrous THF, cooled to 0ºC and under nitrogen atmosphere in order to synthesize the compound **154** (**Scheme 52**).



Scheme 52

Further, the compound **154** withstands a dehydrogenation reaction in the presence of the Wilkinson catalyst [chlorotris(triphenylphosphine)rhodium(I)] and a mixture of dry solvents according to a procedure adapted from literature[7] (**Scheme 53**).

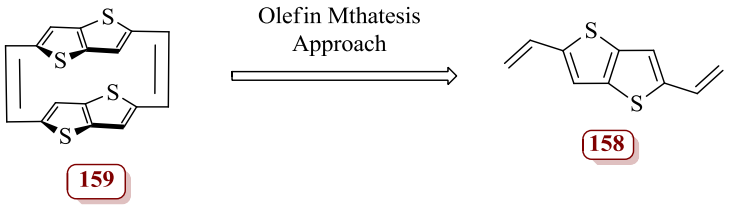


Scheme 53

Due to the difficulties of the dehydrogenation and the very small yields we reconsider this strategy.

2.1.2.b. Metathesis strategy

We suppose that subjecting divinyl-thienothiophene to a metathesis process followed by reduction could be another way to obtain the target cyclophane.

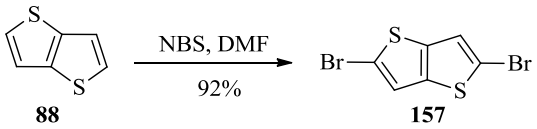


Scheme 55: Olefin metathesis strategy to access thienothiophene-cyclophane

In order to apply a metathesis strategy, first we need to prepare the divinyl-thienothiophene. We succeeded to obtain this derivative in a two-step reaction. Thus, we used compound **88** in a

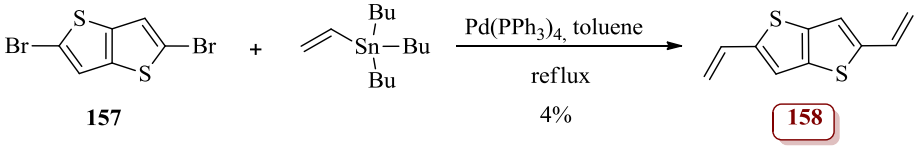
[7] Hornfeldt, A. B., Gronowitz, J. S., Gronowitz, S. *Acta Chem. Scand.* **1968**, *22*, 2725

bromination reaction with NBS in the presence of dimethylformamide as solvent under nitrogen atmosphere at 0ºC (**Scheme 60**).



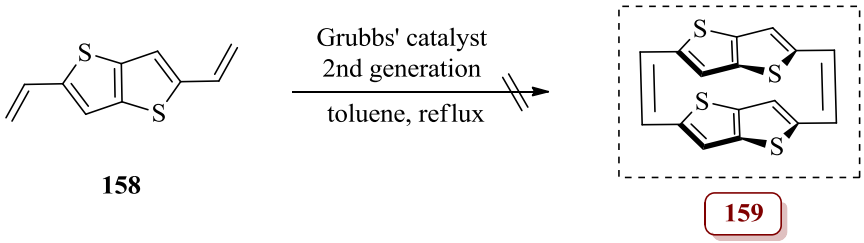
Scheme 60

In the next step we used the dibromo derivative **157** in a Stille reaction with tributhyl(vinyl) stannane and tetrakis(triphenylphosphine) palladium (0) catalyst in anhydrous toluene (**Scheme 61**).[8]



Scheme 61

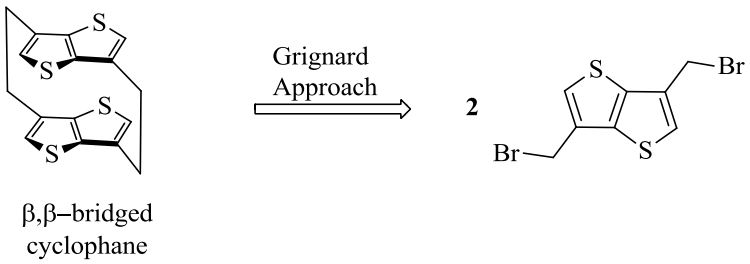
Now that we have the *building block* of the proposed strategy, respective divinyl derivative was subjected to a metathesis reaction. Using the 2nd generation Grubbs catalyst we expect formation of a double intramolecular cyclisation of compound **158** after a describe method in the literature (**Scheme 62**).[9]



Scheme 62

2.2. β-β BRIDGED CYCLOPHANES

2.2.1.a. Grignard Strategy

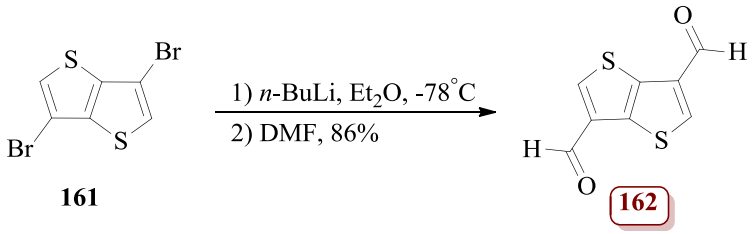


Scheme 63

[8] Gajare, A. S., Jensen, R. S., Toyota, K., Yoshifuji, M., Ozawa,F. *Synlett* **2005**, *1*, 144
[9] Leriche, P., Blanchard, P., Frere, P., Levillain, E., Mabon, G., Roncali, J. *Chem Comm.* **2006**, 275

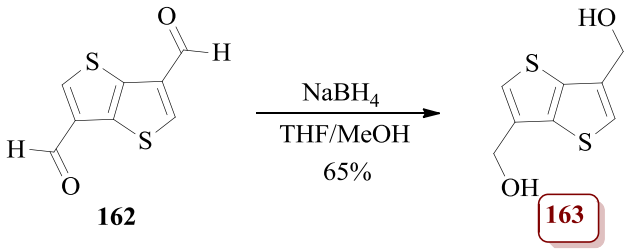
Thus, 3,6-di(bromomethylene)-[3.2-*b*]thienothiophene was prepared in a three-step procedure starting from 3,6-dibromothieno[3,2-*b*]thiophene as follow: 1-formylation, 2-reduction to alcohol and 3-bromitaion.

Using 3,6-dibromothieno[3,2-*b*]thiophene and *n*-BuLi at -78ºC in anhydrous diethyl ether under inert atmosphere. The new dialdehyde **162** was obtained in 86% yield (**Scheme 65**).



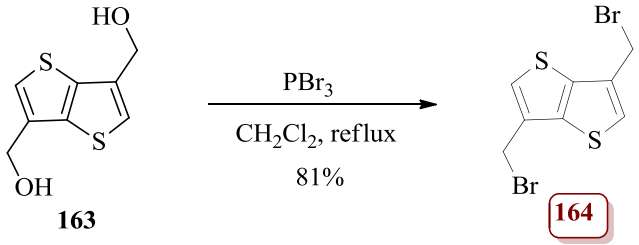
Scheme 65

Following step consist in a reduction reaction of dialdehyde **162** using sodium borohydride and a mixture of THF and MeOH as solvent.



Scheme 66

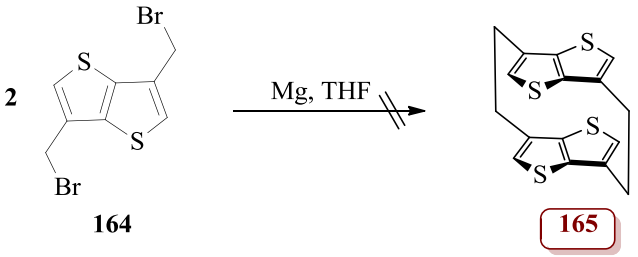
In the third step derivative **163** was involved in a bromination reaction with phosphorus tribromide in dry dichloromethane under inert atmosphere (**Scheme 67**).



Scheme 67

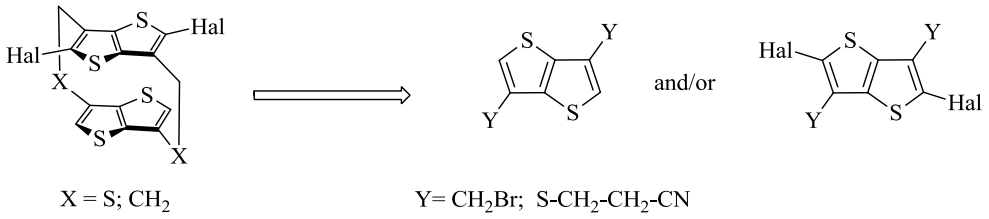
With our dibromoderivative **164** in hands and adapting a literature procedure[10] we intend to perform a cyclisation reaction in presence of metallic magnesium in anhydrous tetrahydrofurane under inert atmosphere (**Scheme 68**). The NMR investigation done after the work-up of the reaction mixture showed that resulted solid was the starting material.

[10] Sato, M-A, Sakamoto, M-A, Miwa, M., Hiroi, M *Polymer* **2000**, *41*, 5681



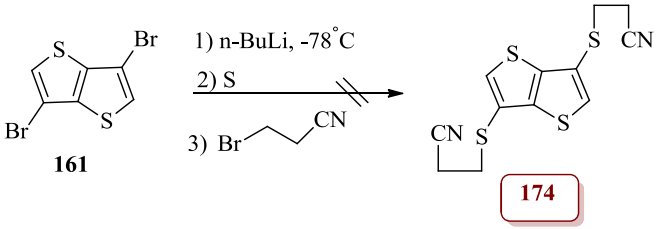
Scheme 68

2.2.1.b. The synthesis of β-β cylclophanes via sulphide linkage



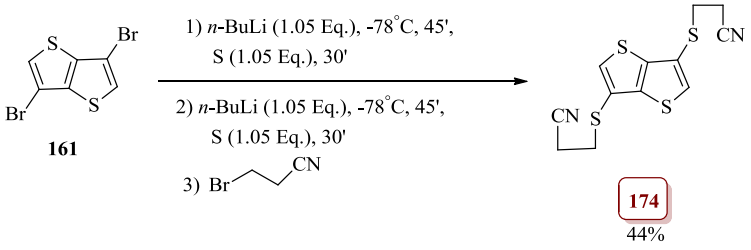
Scheme 70

Using the dibromo-TT derivative **161** in a lithiation reaction with *n*-BuLi at -78ºC in anhydrous diethyl ether under inert atmosphere (**Scheme 78**). At the end we recover only the starting material, thus the first attempt to obtain the thiol derivative failed.



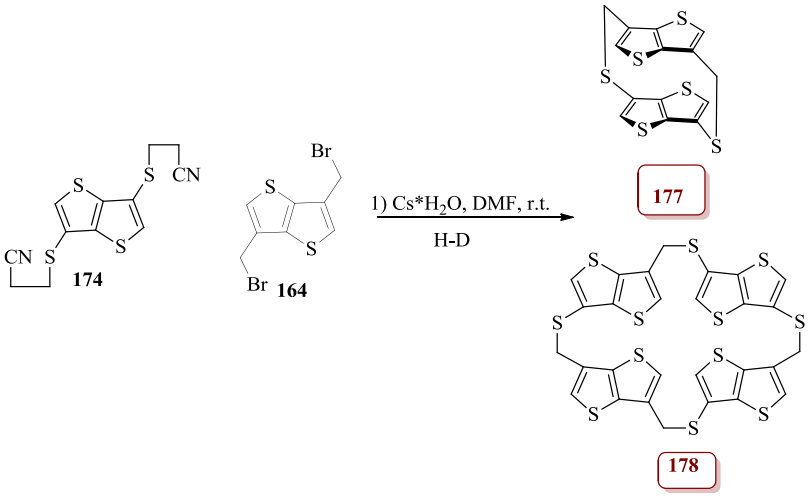
Scheme 78

Due to the fact that the first attempt of lithiation wasn't successful we perform a new lithiation reaction, the difference between the two procedures consists in gradual change of Br/Li. Therefore in the first part we added only 1.05 Eq. of *n*-BuLi and sulfur and kept the temperature at -78ºC for 45 minutes, after this period we added the rest of the *n*-BuLi and sulfur (**Scheme 79**). This approach had the expected final results; the structure of the derivative was proved by NMR investigations.



Scheme 79

Considering the fact that we synthesized derivative **174** and the bromomethyl-TT **164** we involve them in a two step macrocyclisation: 1) deprotection of derivative **174** in presence of cesium hydroxide in anhydrous DMF at room temperature and under inert atmosphere (similar method used in deprotection of derivative **152** see **Scheme 48**); 2) reaction between deprotected **174** and dibromomethyl-TT **164** in high dilution conditions (**Scheme 83**).



Scheme 83

The structure of the two new derivatives was confirmed by MALDI analysis.

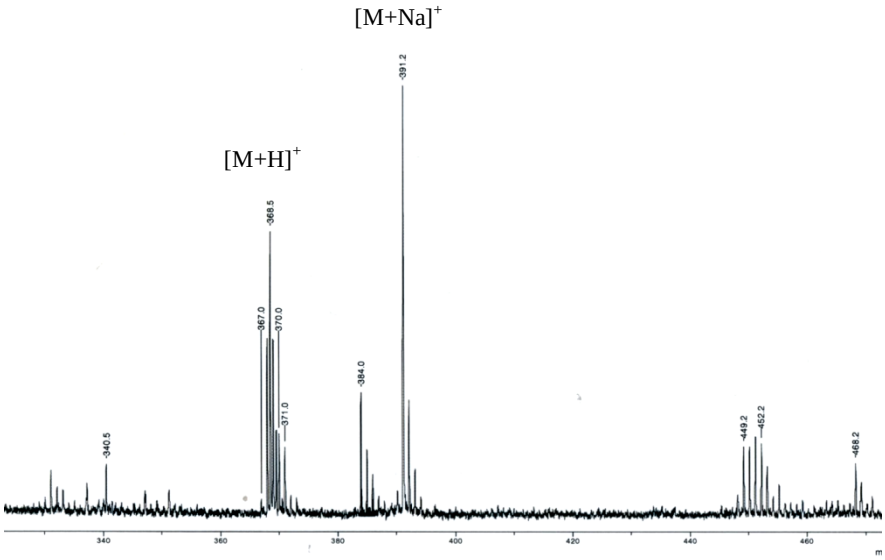


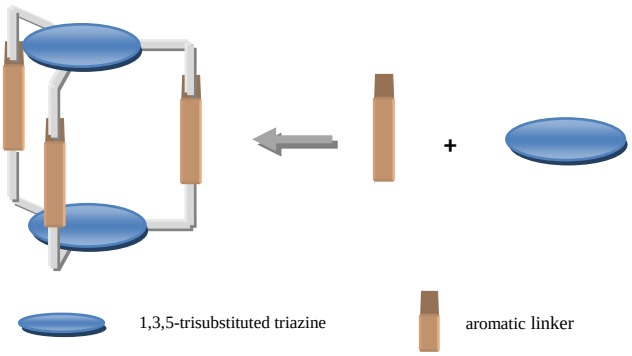
Figure 32: MALDI-TOF of derivative **179**

PART II: *PRECURSORS FOR CAGE MOLECULES WITH TRIAZINE UNITS*

Key Words: cryptand, 1,3,5-tris(phenyl)triazine

2. ORIGINAL CONTRIBUTIONS

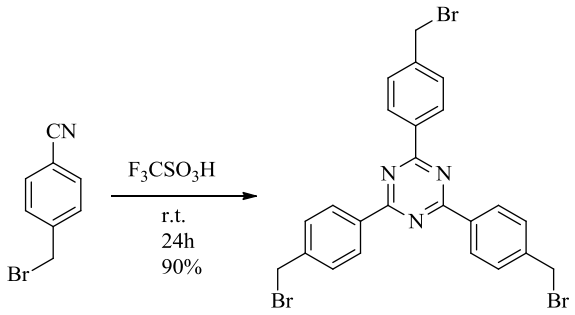
The main goal of the second part of thesis is the synthesis of new macrocycles having C_3 simmetry and 1,3,5-tris(phenyl)-2,4,6-triazine units according to the following retrosynthetic analysis (**Scheme 3**).



Scheme 3

Therefore, the initial steps in obtaining of new cage molecules required the synthesis of some 1,3,5-trisubstituted triazine derivatives.

4-(bromomethyl)benzonitrile **15** was converted into compound **16** (**Scheme 7**).[11] We mention that we managed to improve the yield of this reaction by using the triflic acid in excess.[12]

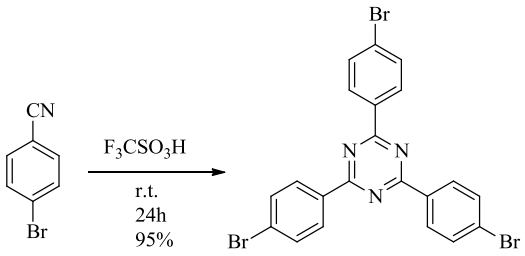


15 **16**

Scheme 7

Using similar reaction conditions was obtained the compound **18** in very good yield using 4-bromobenzonitrile as a starting material (**Scheme 8**).

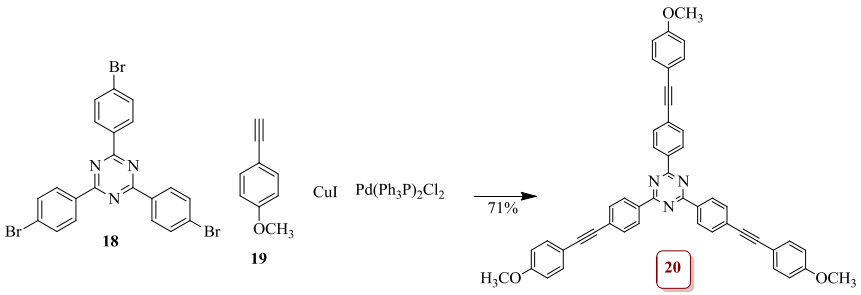
[11] Punidha, S., Sinha, I., Kumar, A., Ravikanth, M. *J. Org. Chem.* **2008**, *73*, 323
[12] Woiczechowski-Pop, A.; Dobra, I. L.; Roiban, G. D.; Terec, A.; Grosu, I. *Synth. Commun.* **2012**, *42*, 3579



17 **18**

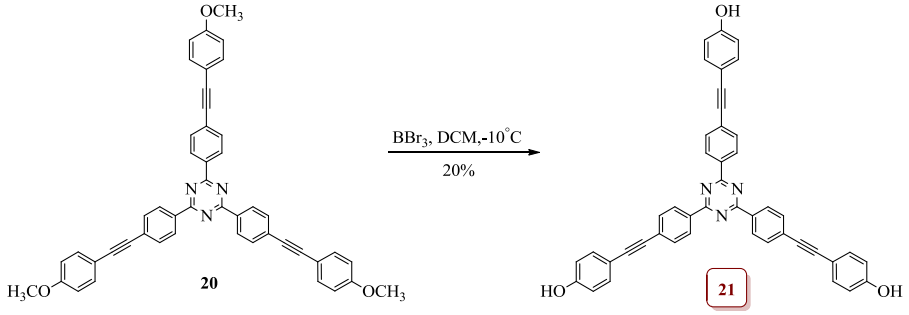
Scheme 8

Due to the fact that our goal is not only the synthesis of new cage molecules, but also the synthesis of cage molecule having the dimension of cavity bigger in order to attempt complexation with different molecules, we tried to obtain some new spacers with triazine units. Thus, we synthesized the spacer **20** using as starting material derivative **18** and compound **19** (**Scheme 9**). The Sonogashira coupling was performed according with a procedure described in literature.[13]



Scheme 9

Following step consist in a demethylation reaction of the derivative **20**, normally we would used the procedure which use pyridine hydrochloride at 200°C,[14] but this time we change the procedure and used boron tribromide as demethylation agent (**Scheme 10**).[15]



Scheme 10

[13] Hennrich, G., Ortiz, P. D., Cavero, E., Hanes, R. E., Serrano, J. L. *Eur. J. Org. Chem.* **2008**, 4575
[14] Constable, E. C., Housecroft, C. E., Neuburger, M., Poleschak, I., Zehnder, M. *Polyhedron* **2003**, *22*, 93
[15] a) Gevorgyan, V., Quan, L. G., Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 12445; b) Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427

GENERAL CONCLUSIONS

This thesis has two different part and concerns. The first part deals with the in developing the fundamental methodology necessary to construct such type of stacked [n.n]paracyclophane possessing thienothiophene as aromatic units.

In order to achieve the propose goal we approach by two different ways:

- attempting to synthesized α-α bridged cyclophanes;
- and β-β bridged cyclophanes having as central unit thieno[3,2-*b*]thiophene.

The first strategy was applied to obtain new α-α bridged cyclophanes, in order to afford this type of cyclophanes more synthetically strategies were employed. Although we didn't synthesized the target molecule we managed to obtained three new derivatives.

On the way, new derivatives of thieno[3,2-*b*]thiophene (10) were obtained and used as precursors for the synthesis of the target cyclophanes.

Different methods were adapted in order to afford the dialdehyde **163**, this methods finalized with the obtaining of three new thieno[3,2-*b*]thiophene.

The second strategy applied to synthesized β-β bridged cyclophanes was completed with the obtaining of two types of macrocylic compounds: a new β-β bridged cyclophanes and a new macrocyle having as central unit thieno[3,2-*b*]thiophene.

We mention that two new derivatives were analyzed by X-ray diffraction (**163** and **176**).

The second part of the thesis has as target the new macrocycles having C_3 symmetry and 1,3,5-tris(phenyl)-2,4,6-triazine units. In this part we present the synthesis and analysis of two new derivatives having C_3 symmetry which will be further used for building new cage molecule with 1,3,5-tris(phenyl)-2,4,6-triazine units.

We adapted the procedure already described in the literature for the synthesis of derivatives **16** and **18** and we improved the yields of these reactions by using the triflic acid as solvent and as reagent.

A part of the results presented in the second part were already published.